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ORIGINAL ARTICLE

Facial granulomatous dermatoses: A clinico-pathological study

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Abstract *Background:* Granulomatous dermatoses frequently present a diagnostic challenge as an identical histologic pattern may be produced by several causes, and conversely, a single cause may produce several histologic patterns. The present study aims at diagnosing facial granulomatous dermatoses based on combination of clinical and histopathological features and evaluating their correlation.

Methods: Archival records were retrieved and clinically suspected and/or histopathologically diagnosed facial granulomatous dermatoses cases were taken as study material. Clinical and histopathological data was tabulated and concordance rate was calculated.

Results: Out of 832 skin biopsies, 64 were from face and 18 were of facial granulomatous dermatoses. Age ranged 13–55 years with male to female ratio 1.6:1. Majority (88%) were of infectious etiology, leprosy being maximum i.e. 10/18 cases (55%) and borderline tuberculoid outnumbered all other categories with 7/10 cases (70%). Histopathologically, 14 cases (77.78%) had epithelioid granulomas and two each of histiocytic and mixed inflammatory type. Ziehl–Neelsen stain was positive in three cases (16.67%). Overall clinico-pathological concordance rate was 61.11% with 77.77% concordance for leprosy cases.

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Conclusion: Major cause of granulomatous diseases in developing countries is still infection. Clinicohistopathological constellation is important to pinpoint a diagnosis to mete out appropriate treatment.

1. Introduction

Granulomatous dermatoses comprise patterns of reaction to various organic and inorganic antigens. The granulomatous reaction is defined as a distinctive inflammatory pattern characterized by the granulomas. (Weedon, 2003) According to the current concept, 'granuloma' is defined as a focal chronic inflammatory response to tissue injury characterized by a collection of activated histiocytes, epithelioid cells and multinucleate giant cells that may or may not be rimmed by lymphocytes and/or show central necrosis (Hirish and Jhonson, 1984).

Granulomatous dermatoses form a common and intriguing problem. Histopathology remains a time-tested tool for establishing the correct diagnosis like in many other diseases pertaining to various organ systems of the body (Dhar and Dhar, 2002). However, these dermatoses frequently present a diagnostic challenge as an identical histologic pattern may be produced by several causes, and conversely, a single cause may produce several histologic patterns (Zaim et al., 1990). Differential diagnosis and management of these dermatoses thus demand a skillful interpretation of both clinical findings and histology (James and Zumla, 1999).

Clinically, granulomatous dermatoses may involve any part of the body with different predilection sites for different conditions. Usually, lesions are long standing and tend to heal with some amount of scarring as the pathology involves the dermis. Though, lesions anywhere on the skin alarm the patient due to the associated cosmetic disfigurement, facial skin is the priority cosmetic concern of every individual. The present study focuses on the clinical and histopathological features of granulomatous lesions present on the face.

The present study aims at diagnosing facial granulomatous dermatoses based on a combination of clinical and histopathological features, and evaluating the correlation between clinical suspicion and histopathological suggestion, thus highlighting the significance of clinico-pathological correlation in making the final diagnosis.

2. Materials and methods

The present study is a retrospective analysis of facial skin biopsies submitted to the department of Pathology, Era's Lucknow Medical College and Hospital, Lucknow, India over a period of two years (July 2010–June 2012). Archival skin biopsy records were retrieved and clinically suspected and/or histopathologically diagnosed cases of granulomatous dermatoses were taken as study material. Lesions of oral mucosa were excluded from the study. Patient's age, sex, clinical history, findings, differential diagnosis and other relevant data were recorded for each case. In all the cases, histopathological features were studied on hematoxylin and eosin stained slides. Relevant special stains like Ziehl-Neelsen (ZN), modified ZN, periodic acid schiff (PAS), Grocott, Gram, Giemsa, etc. were performed as per the individual case diagnostic implication. The slides were examined under the light microscope and detailed histopathological features of ''Granuloma'' i.e. location in relation to dermis, type, accompanying cell population and epidermal changes were studied. Complete clinical and histopathological data were carefully tabulated and clinico-pathological correlation was established. Concordance rate between clinical and histopathological diagnosis was calculated.

3. Results

During the two year time period of our study, a total of 832 skin biopsies were received in the department of pathology. Only 64 of the total 832 skin biopsies were from the face. Out of the 64 facial skin biopsies, 18 cases were of granulomatous dermatoses clinically and/or histopathologically. Out of a total of 18 cases, 11 (61.11%) were males and 7 (38.89%) were females with a male to female ratio of 1.6:1. Age of the patients ranged from 13–55 (mean 27.38) years.

All the cases were of benign etiology. Majority of cases i.e. 16 out of 18 cases (88%) were of infectious etiology. Leprosy cases were maximum in number i.e. 10 out of 18 cases (55%) and further sub-classification according to Ridley and Jopling revealed that borderline tuberculoid (BT) had outnumbered all other categories with seven out of 10 cases (70%) (Fig. 1a). Mid borderline (BB) (Fig. 1b), borderline lepromatous (BL) and lepromatous leprosy (LL) (Fig. 1c) accounted for one case (10%) each of total leprosy cases. Cutaneous tuberculosis was revealed in four cases (22%) and all were of lupus vulgaris. There was one case (5.56%) each of actinomycosis and cutaneous leishmaniasis. Out of two cases of unknown etiology, one had sarcoidosis and the other patient had granulomatous rosacea.

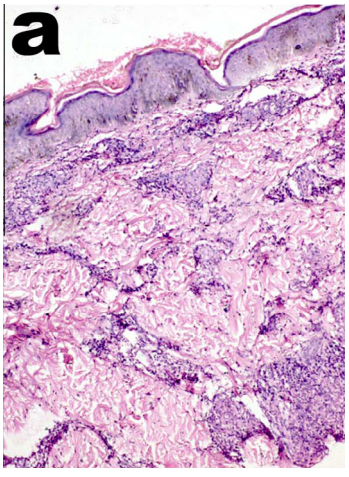

Figure 1a Borderline tuberculoid leprosy- dermis shows many non-caseating epithelioid cell granulomas distributed in periadnexal and perineural location (H & E 10×).

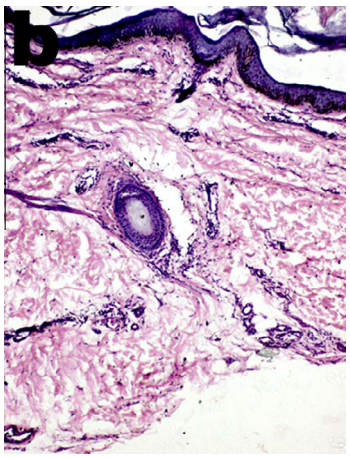

Figure 1b Mid borderline leprosy- characteristic distribution of lymphohistiocytic infiltrate is seen around adnexa and vessels (H & E 10×).

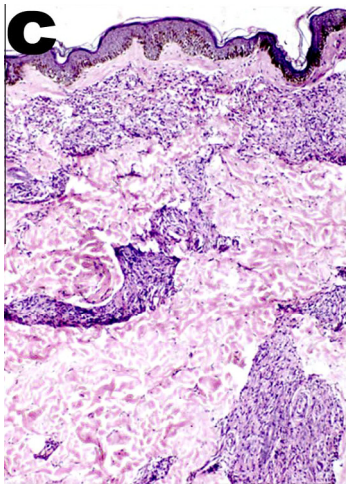

Figure 1c Lepromatous leprosy- dermis shows a mass of foamy macrophages, with no granuloma formation. Clear grenz zone is appreciable under the epidermis. (H & E 40×).

Histopathologically, 14 cases (77.78%) had epithelioid granulomas with 12 (66.67%) tuberculoid and two (11.11%) sarcoidal granulomas. Two cases (11.11%) had mixed inflammatory granuloma, out of which one case (5.56%) had suppurative granuloma and the other had plasma cell rich infiltrate. None of the cases had foreign body or necrobiotic granuloma.

Ziehl–Neelsen stain for acid-fast bacilli (AFB) was positive in three cases (16.67%), out of which one case each was of BL leprosy and LL leprosy (both cases of histiocytic granuloma) (Fig. 1d) and the third had lupus vulgaris (tuberculoid granuloma). PAS and gram stain were positive for actinomycosis (suppurative granuloma) case. Giemsa stain was positive in a case of cutaneous leishmaniasis (CL) for Leishmania-Donovani (LD) bodies. Reticulin stain was positive in the case of sarcoidosis (epithelioid granuloma), highlighting pattern of confluent granulomas, further supporting the diagnosis.

Clinically eight cases were classified as hansen's disease; out of which four were classified as BT, two as BB and two as LL/

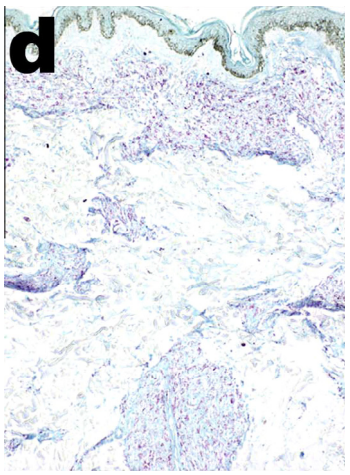

Figure 1d Large number of solid acid-fast bacilli are seen in macrophages which are arranged in globi in the dermis (AFB 40×).

BL. Of the four cases diagnosed clinically as BT, three were confirmed on histopathology as BT and ones was diagnosed as BB. Clinico-pathological concordance was thus 75% for clinically diagnosed BT cases. Two cases classified clinically as BB leprosy were confirmed as BT on histopathology with 0% clinico-pathological parity. Of the two cases which proved to be a clinical dilemma between BL and LL, one was confirmed as BL and other as LL thus establishing 100% concordance. AFB were seen lying individually and in globi in BL and LL cases respectively. Of the two cases clinically diagnosed as LV, one was confirmed as LV but the other turned out to be BT leprosy on histopathology, with a 50% clinico-pathological concordance rate. Two cases which were classified as DLE clinically, were confirmed as LV histopathologically. Thus, for DLE lesions the clinico-pathological parity was 0%. A single case in which clinical differential diagnosis of both LV and DLE was made had LV on detailed histopathology. There were two cases which were clinically diagnosed as sarcoidosis, out of which one was confirmed as sarcoidosis while the other showed features of BT leprosy histopathologically. One case each of actinomycosis and cutaneous leishmaniasis was correctly diagnosed on the basis of clinical presentation and confirmed on HP, thus showing a 100% clinico-pathological correlation. One case was a clinical dilemma between GR, BT, LV and sarcoidosis. On histopathology, it was confirmed as granulomatous rosacea (GR) due to typical features.

The clinical and histopathological details and concordance rates between the clinical and histopathological diagnoses have been tabulated. (Table 1)

4. Discussion

The term "granuloma" is derived from the Latin "granulum" referring to a small particle such as grain. Originally thought to represent a neoplastic growth of granulation tissue, "granuloma" now implies a reactive, non neoplastic, inflammatory tissue reaction (Pinkus and Mehregan, 1981). Granulomas form as a response to insoluble, nondegradable, or slowly released antigens which cause transformation of histiocytes into activated macrophages, epithelioid cells and multinucleate giant cells. As they transform, histiocytes replace phagocytic

Table 1 Clinical and histopathological details and concordance rates.

Case no.	Age	Sex	Clinical details	Histopathological details	Etiological classification	Concordance/Parity%age	AFB					PAS/ Grocott stain for fungus	Giemsa stain	Gram stain	Reticulin stain
			Clinical Diagnosis	Lesion description	HP Diagnosis	Features of granuloma Type	Location	Epidermis							
1	13	M	BT	2–10 large, well defined, dry, hypoesthetic, hypotrichotic, hypopigmented, indurated plaques	BT	Epithelioid, non-caseating	Upper dermis	Atrophic	Infectious (M leprae)	75	A	ND	ND	ND	ND
2	24	M	BT		BT	Epithelioid, non-caseating	Upper dermis, periadnexal	UR	Infectious (M leprae)		A	ND	ND	ND	ND
3	43	M	BT		BB	Epithelioid, non-caseating	Upper & mid dermis	UR	Infectious (M leprae)		A	ND	ND	ND	ND
4	35	F	BT		BT	Epithelioid, non-caseating	Upper dermis	Atrophic	Infectious (M leprae)		A	ND	ND	ND	ND
5	28	M	BB	8 and 14 medium sized, well defined, erythematous, plaques	BT	Epithelioid, non-caseating	Upper dermis, periadnexal & perineural	Atrophic	Infectious (M leprae)	0	A	ND	ND	ND	ND
6	36	F	BB		BT	Epithelioid, non-caseating	Upper dermis, periadnexal	UR	Infectious (M leprae)		A	ND	ND	ND	ND
7	30	F	BL/LL	Numerous, ill-defined, hypopigmented macules. Glove and stocking anesthesia	BL	Histiocytic	Upper & mid dermis, narrow grenz zone present	Atrophic	Infectious (M leprae)	100	P	ND	ND	ND	ND
8	42	F	LL/BL		LL	Histiocytic	Mid dermis, clear broad Grenz zone present	Atrophic	Infectious (M leprae)		P	ND	ND	ND	ND
9	16	F	LV	Two well defined, erythematous, indurated plaques	BT	Epithelioid, non-caseating	Upper dermis, periadnexal	UR	Infectious (M leprae)	50	A	ND	ND	ND	ND
10	24	M	LV	Single well defined, brownish red, indurated plaque with apple jelly nodules	LV	Epithelioid, non-caseating	Upper dermis	Atrophic, and hyperplastic partly	Infectious(M tuberculosis)		A	ND	ND	ND	ND
11	28	M	DLE	Single, well demarcated, erythematous, infiltrated plaque with slight atrophy	LV	Epithelioid, non-caseating	Upper & mid dermis	Atrophic	Infectious(M tuberculosis)	0	P	ND	ND	ND	ND
12	36	M	DLE		LV	Epithelioid, caseating	Upper dermis	Atrophic	Infectious(M tuberculosis)		A	ND	ND	ND	ND
13	26	F	LV/DLE	Two, well defined, erythematous, indurated plaque with areas of scarring and hypertrophy	LV	Epithelioid, non-caseating	Mid dermis	Atrophic, and hyperplastic partly	Infectious(M tuberculosis)	100	A	ND	ND	ND	ND
14	32	F	Sarcoidosis	Well defined, brownish-red, indurated, edematous, plaque on nose	BT	Epithelioid, non-caseating	Upper dermis, periadenexal	Atrophic	Infectious(M leprae)	50	A	ND	ND	ND	A
15	38	M	Sarcoidosis	Multiple, small, edematous, purplish-red, papules on nose and preauricular area	Sarcoidosis	Naked Epithelioid, non-caseating	Dermis & subcutis	UR	Unknown		A	ND	ND	ND	P
16	42	M	Actinomycosis	Sinus discharging pus and sulfur granules on the left mandibular area	Actinomycosis	Suppurative	Throughout dermis	Focally ulcerated	Infectious(Actinomycosis species)	100	A	P	A	P	ND
17	55	M	GR/ BT/ LV/ Sarcordosis	Single, large, well-defined, erythematous, smooth, shiny plaque	GR	Epithelioid, non-caseating	Upper & mid dermis, around pilosebaceous units	UR	Unknown	100	A	A	A	A	A
18	27	M	Cutaneous Leishmaniasis	Single, asymptomatic, erythematous plaque with 2 small ulcers	Cutaneous Leishmaniasis	Mixed inflammatory (Plasma cell rich)	Throughout dermis	Hyperplastic and focally ulcerated	Infectious (Leishmania)	100	A	A	P	A	ND

F:Female, M:Male, UR:Unremarkable, A:Absent, P:Present, ND:Not done, BT:Borderline tuberculoid, BB:Midborderline, BL:Borderline lepromatous, LL:Lepromatous, leprosy, LV:Lupus vulgaris, DLE:Discoid lupus erythmatosis, GR:Granulomatous Rosacea, Overall concordance between clinical and histopathological diagnosis in 18 cases is 61.11%.

activity with secretory function, gaining the ability to recruit additional macrophages, and mediate fibroplasia and collagen deposition (Furth et al., 1977). Fully developed granulomas with sheets of epithelioid histiocytes and giant cells are easily recognized, but more subtle lesions containing a few epithelioid histiocytes still qualify as granulomatous (Rabinowitz and Zaim, 1996).

Granulomatous lesions are a part of chronic inflammatory process spectrum which results in varied clinical presentation and histopathologic presentation with a wide diversity in the microscopic appearance. Clinical lesions often reveal surprising underlying pathology. Hence, carrying out skin biopsies and microscopic study with routine hematoxylin and eosin (H&E) as well as special stains is must in these disorders so that the type and etiologic agent of the granuloma are correctly identified (Lever and Schaumberg-Lever, 1997).

It is difficult to present a completely satisfactory classification of the granulomatous reaction. It has been classified on the basis of etiology, pathophysiology, immunology and histopathology. Based on the presence or absence of an infectious pathogen that serves as the inciting antigen it is etiologically classified as infectious or non-infectious. Infectious granulomatous dermatoses may be easier to diagnose and treat as the inciting microorganism can be identified. While many granulomatous responses have traditionally been regarded as non-infectious, it is important to acknowledge the proposed role for infection in the etiology of several of these conditions that are regarded as 'non-infectious' granulomatous disorders, such as a slow-growing infection, (Mohan and Bal, 2004; Rook and Stanford, 1992) a post-infectious immunologic response, or presentation of granulomatous disease in the setting of infection (Dzirlo et al., 2007 May 26). Further, it is also possible that these diseases represent a cutaneous expression of infective states mediated by the immune system, such as reactive erythemas or the id reaction (Magro and Crowson, 1998). Thus, for many of these conditions, we have a poor understanding of the inciting antigen, which may range from infectious (including live or dead microorganisms) to drugs (and/or their metabolites), or result from innate host pathology (e.g. connective tissue disease, vasculitis, or cancerous antigens).

Histopathological diagnosis is assisted by categorizing the granulomatous reaction pattern into five distinct types on the basis of the constituent cells and other changes within the granulomas Rabinowitz and Zaim, 1996).

(1) Epithelioid granulomas (tuberculoid and sarcoidal), (2) Histiocytic granulomas, (3) Necrobiotic/palisading granulomas, (4) mixed inflammatory granulomas (suppurative granulomas), (5) Foreign body granulomas.

Histopathological examination of the three clinically diagnosed cases of BT, two cases of BB, one case each of LV and sarcoidosis revealed well formed epithelioid cell granulomas in upper dermis not encroaching upon the epidermis with mild mononuclear infiltrate and occasional giant cells. Granulomas of tuberculoid (TT) and borderline tuberculoid (BT) leprosy are epithelioid granulomas with Langhans and foreign body giant cells and thus requires differentiation from sarcoidosis and non-caseating tuberculous granulomas (Hirish and Jhonson, 1984; Young et al., 2001). In such cases, lepra stain is not of much help because of sparse bacilli (Cree et al., 1990). However, location of granulomas around neurovascular bundle, erector pili muscle and adenexa in combination with clinical picture is helpful. Thus, these cases were diagnosed as BT leprosy.

One case clinically diagnosed as BT which turned out to be BB leprosy histopathologically, showed characteristic distribution of lymphohistiocytic infiltrate around adnexa and vessels. Giant cells and foamy cells were absent.

The case having granuloma rich in foamy histiocytes and numerous lymphocytes with a barely perceptible grenz zone was diagnosed as BL; and the one with diffuse sheets of foamy histiocytes, very few lymphocytes and a clear grenz zone was classified as LL. Borderline lepromatous (BL) and lepromatous leprosy (LL) are characterized by histiocytic granulomas and are strongly positive for lepra bacilli, (latter showing plenty of bacilli in globi) thus posing no difficulty in diagnosis.

Of the total 10 cases confirmed as leprosy on histopathology, eight cases were correctly diagnosed as leprosy clinically and the classification was concordant in five cases. Thus, there was a good (80%) clinicohistological correlation as far as the diagnosis of leprosy is concerned, but the correlation was poor (50%) for sub-typing. This may be due to the fact that histological changes may precede the appearance of clinical lesions owing to a highly unstable immunological status of leprosy patients especially those with borderline leprosy (Sehgal et al., 1980; Ridley, 1974; Ridley and Jopling, 1966).

Of the three clinically diagnosed cases of LV, one was of BT leprosy and the rest two were confirmed as LV on histopathology. Two other cases clinically diagnosed as DLE had histopathological features consistent with LV and showed epithelioid cell granuloma in the upper-mid dermis with smattering of Langhans giant cells and liberal lymphocytic rimming of the granulomas. The epidermis was atrophic in all the four cases and had areas of hyperplasia in two cases. AFB could be demonstrated in only one case. Confirmed diagnosis of cutaneous tuberculosis requires evidence of the presence of the tubercle bacilli either in the smear or in the tissue section or its recovery in vitro (Lever and Schaumburg-Lever, 1983). However, AFB by ZN are not detected with ease and the literature has reported 13–15% positivity in lupus vulgaris (25% in present study) and up to 50% positivity in scrofuloderma. Establishment of the diagnosis in cutaneous tuberculosis is therefore achieved by the correlation of the various relative and absolute criteria (Marcoval et al., 1992; Sehgal and Wagh, 1990).

Only two cases were clinically diagnosed as DLE and on histopathology both had features suggestive of LV. An interesting conclusion which can be derived is that LV over the face can masquerade as DLE and this reiterates the importance of histopathology for correct diagnosis. Similar observation was made by Dhar et al. Dhar and Dhar (2002). Of the total four confirmed cases of LV, only two were correctly diagnosed clinically thereby establishing a clinico-pathological concordance of 50% for the diagnosis of LV.

Two cases were diagnosed clinically as sarcoidosis, of which one showed histological changes of BT. The other case had well demarcated, variable sized islands of epithelioid cells with a few Langhans type giant cells and only sparse lymphocytic infiltration. Reticulin stain highlighted the confluent granuloma pattern. Histopathology of sarcoidosis resembles TT and BT leprosy but in latter the granulomas are centered around neurovascular bundle characteristically. Some of the foreign body reactions present with similar granulomas; however, polarizing foreign body can be identified in the giant cells (Millet et al., 1987). Cutaneous sarcoidosis may occur at any

stage of the disease but most often it is present at the onset of disease and is known as one of the "great imitators" in dermatology as lesions may assume a vast array of morphologies, masquerading as a wide range of disorders from benign appendageal growths to malignant Kaposi sarcoma (Newman et al., 1997; Mana et al., 1997; Katta, 2002; Thaipisuttikul and Kateruttanakul, 2007).

There was only one case of actinomycosis which presented as a red, indurated, non-tender subcutaneous mass in the left mandibular region. Histopathology revealed suppurative granuloma with dense inflammation, extensive fibrosis and presence of sulfur granules. The epidermis was focally ulcerated. The organism could be demonstrated by PAS and gram stain. Thus, the diagnosis of actinomycosis was confirmed and there was a 100% clinico-pathological correlation. Fungal infections are characterized by mixed/suppurative granulomas (Sehgal et al., 1980). Demonstration of fungal spores/hyphae with the help of special stains like PAS and Gomori's methenamine is confirmatory (Hiruma et al., 1992).

One case which was a clinical dilemma between GR, LV, BT leprosy and sarcoidosis was confirmed as GR. Granulomatous rosacea can mimic various facial granulomatous conditions both clinically and histologically, such as lupus miliaria disseminatus faciei, micropapular sarcoidosis, and cutaneous tuberculosis. But in our case, the differential diagnoses were GR, sarcoidosis, BT Hansen, and LV because of the unusual presentation as a solitary plaque. Histopathology came to our rescue and revealed non-ceseating epitheloid granulomas with lymphohistiocytic infiltrate centered around the pilosebaceous units which was suggestive of granulomatous rosacea. This established a 100% clinico-pathological correlation (Patrinely et al., 1990; Batra et al., 2011).

Clinically diagnosed case of cutaneous leishmaniasis (CL) was confirmed on histopathology as it revealed ill formed, mixed inflammatory granulomas with plenty of plasma cells. Giemsa staining revealed recognizable Leishmania Donovani (LD) bodies in the surrounding tissue. It has been well recognized that there is a clinical and histological spectrum in cutaneous leishmaniasis. The spectrum and its variability are dependent on a number of factors such as the type and duration of clinical lesion, strain of organism, geographic location, parasitic load, host immunity etc (Grevelink and Lerner, 1996). Once restricted to certain areas, it is now spreading to places that were previously known to be nonendemic and new foci of infection are regularly being encountered in Pakistan as well as in India. In an endemic area, CL can generally be diagnosed by its clinical appearance alone (Raja et al., 1998; Herwaldt, 1999; Grevelink and Lerner, 1996; Lahiry, 2002). Definite diagnosis of cutaneous leishmaniasis however is based on the isolation of the causative organism by smear and culture or its identification in tissue section (Kaur et al., 2003). In the present case, the diagnosis was confirmed due to identification of the causative organism. Thus, for this single case of cutaneous leishmaniasis we could establish a 100% clinico-pathological correlation.

In the present study, an overall clinico-pathological concordance rate of 61.11% was established. In the study by Dhar et al. (Dhar and Dhar, 2002) the clinico-pathological concordance rate was 77.27%. Our study had relatively lower rates of clinico-pathological concordance probably because we had relatively more cases of leprosy than in the latter study (55% vs 40.9%) where immunological status is not stable. If we consider only leprosy and exclude the typing, the clinico-pathological concordance rate for our study is 77.77% which is similar to that of Dhar et al Dhar and Dhar (2002).

5. Conclusion

The major cause of granulomatous diseases in developing countries is still infection, unlike the spectrum in the developed world, which is either autoimmune or due to other causes (Rabinowitz and Zaim, 1996) The classical clinical features may be absent and identifying the etiological agent may not always be possible. Morphology alone is seldom specific and cannot be used as a diagnostic tool for identification of specific diseases. A clinico-pathological correlation offers the most secure foundation for establishing the diagnosis. A constellation of clinical features noted by the clinician and histopathological features noted by the pathologist is more important for facial granulomatous dermatoses and helps to pinpoint a diagnosis and confirm it.

Conflict of interest

None.

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None.

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